DESIGN OF DRUGS: BASIC PRINCIPLES AND APPLICATIONS

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INTRODUCTION

Drug design and discovery techniques have evolved considerably in recent years but they have progressed in two opposite directions. On the one hand, considerable intellectual and financial efforts have been made to implement a rational sequence of events that would ultimately result in the identification of the successful drug candidate. One of these scenarios is known as "structure-based drug design." At the turn of the millennium, this can be considered as the ultimate stage of development of "rational drug design" (1–4). On the other hand, with the potentialities offered by automated chemical synthesis and robotized biochemistry, the temptation has been ever greater to produce increasingly huge numbers of molecules by combinatorial chemistry techniques and include them in batteries of high throughput screening (HTS). The process of finding novel, active compounds through combinatorial chemistry is akin to finding a needle in a haystack. While per se not irrational, this process can be viewed as using a Monte-Carlo algorithm and as such it can be easily anticipated that convergence in the selection of the successful drug candidate will be inevitably slow. The challenge of the next century will be to reconcile these two approaches to significantly accelerate both discovery and preclinical research. Building a fully integrated, high-throughput drug-discovery platform spanning lead generation through investigational new drugs (INDs) at present remains a critical step to be made in order to efficiently transform proprietary medicinally designed combinatorial libraries into wholly or substantially owned new chemical entities (NCEs).

STRUCTURE-BASED DRUG DESIGN

Historically, the pharmaceutical industry has relied on discovering drug leads by screening-sifting through vast inventories of either naturally occurring or manmade chemicals in search of previously undiscovered substances with the desired biological activity. Traditionally, optimization of a lead compound was achieved by random exploration of a chemical structure (often called lead compound) through the synthesis of large numbers of chemical derivatives. Over the last decade, this approach has become increasingly unsatisfactory, since it is costly and inefficient, and while the rate of discovery of new therapeutic compounds and the marketing of new drugs has declined, the costs have continued to rise. Most importantly, there remain many important therapeutic needs for which screening-based research has failed to yield acceptably safe and effective drugs.

Almost all biologically active molecules work via an interaction with a "target" or "receptor" molecule that plays key roles in all biological processes. In the most common perception of this interaction, the drug molecule inserts itself into a functionally important cleft of the target protein, such as a key in a lock. The molecule then binds there and either induces or more commonly inhibits the protein's normal function. This universal drug-target scheme suggests an interesting alternative approach to drug discovery. Indeed, if it were possible to identify in advance the appropriate protein target for a searched therapeutic need and if enough information were known about the structure of that target protein, it ought to be feasible to design the structure of an ideal drug to interact with it. This approach, called structure-based drug design (5–10), offers the promise of eliminating much of the inefficiency of the classical approaches of conventional drug discovery.

Scientists therefore developed an approach for drug discovery that exploits the 3-D structures of molecular targets (protein structure-based drug design; Fig. 1). At the heart of this strategy is protein X-ray crystallography, which enables one to determine the 3-D atomic structures of target proteins and the drugs that bind to them. This novel approach to drug design integrates genetic engineering techniques that allow the identification, purification, and modification of appropriate target proteins with innovations in protein X-ray crystallography (11–14). This approach also uses elaborated softwares that permit chemists to predict molecular structure in its dynamic and thermodynamic extensions. In contrast to the biotechnology industry, several pharmaceutical groups nowadays employ genetic engineering techniques to produce proteins not as products, but as drug targets. Genetic engineering techniques assist scientists in identifying molecular targets for particular therapeutic objectives, produce target

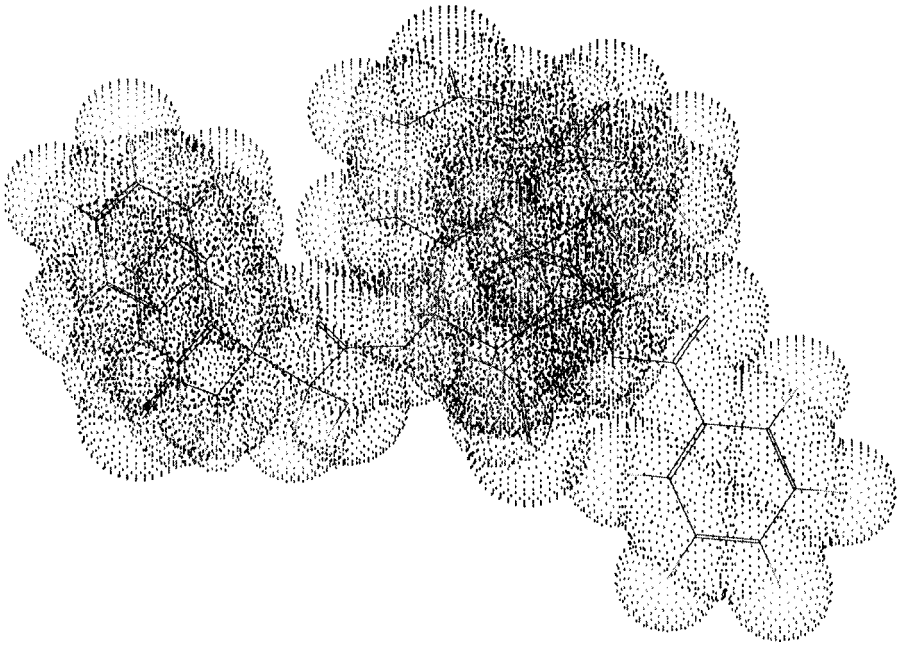

Fig. 1 The 3D vision of pharmacologically active molecules (here taxol) provides the medicinal chemist with a complex information from which a pharmacophore has to be deduced to generate analogs with more adequate pharmocokinetic and toxicological properties.

proteins in sufficient amounts to permit structural studies, and modify these proteins to probe the connections between a target protein's structure and its physiological or pathological functions. So far, the only method that has been successful in determining the precise 3-D atomic structure of large proteins is X-ray crystallography. An important limitation of the method is that X-ray crystallographic studies require a target protein in crystalline form. A powerful X-ray beam bombards a single protein crystal, which diffracts the X-ray beam and generates a definite diffraction pattern. A complex analytical process involving extensive mathematical computations then has to be performed on the X-ray diffraction data. The results of these calculations determine the target protein's exact 3-D structure. It is this information that provides the critical starting point for 3-D drug design. Alternatively, when the target protein cannot be obtained in crystalline form, 2-D nuclear magnetic resonance (2D NMR), or molecular modeling techniques, can provide useful information.

Medicinal chemists and crystallographers begin the process of drug design after determining the 3-D atomic architecture of the target protein and its functionally critical regions. Using a variety of specialized programs on interactive graphics workstations, drug designers generate concepts of drug molecules that complement the unique structure and electronic environment of the target protein. Medicinal chemists then synthesize the most promising candidate structures. As in conventional drug-discovery strategies, biochemists measure the ability of this newly synthesized drug candidate to produce the intended effects on the target protein. Crystallographers then redetermine the structure of the protein target now in combination with the candidate drug molecule included within the active site of the macromolecule. They see the detailed structural interactions actually achieved by the candidate drug with its biological counterpart. Scientists relate the performance of such a compound measured by conventional biochemical or pharmacological techniques to its structural interactions with the target as revealed by X-ray crystallography. The design team then incorporates the results of this analysis into its next generation of compounds. In this scenario, drug-design methodology consists of iterative cycles of simulation, design, synthesis, structure and biological performance assessments, and redesign. The power of this methodology lies in the ability of the drug designers to see the primary event in drug action, i.e., the interaction of the drug with its target as it actually takes place, and guide the design and optimization of drugs by the intimate details of this interaction.

DRUG DESIGN AND CHEMICAL DIVERSITY

In the 1990s, the average cost for introducing a new drug entity to the marketplace was estimated at greater than

$300 million dollars. Of this dollar figure, nearly one-third has been estimated to go to the discovery and optimization of a lead chemical structure. Each compound within a company's archives ultimately finds its origin in the labors of several chemists involved in the synthesis or the isolation and identification of natural products. The cost for the preparation of such compounds on a single-compound basis is very important. It has been estimated that the cost of preparing each novel molecule in the traditional pharmaceutical industry paradigm of individually synthesized molecules prepared in serial fashion is between $5,000 and $10,000. Clearly, an opportunity exists to reduce costs at this earliest stage of the drug-discovery process, i.e., the identification of a novel lead chemical structure (Fig. 2).

Lead structure compounds are currently identified through rational design and/or mass screening. In the past, routine mass screening has been rather successful in identifying new leads. With the recent introduction of high-throughput, automated screening technologies the evaluation of hundreds of thousands of individual test molecules per year against a large number of targets is now feasible. The source of large chemical libraries still remains a stringent limitation. Compound libraries commonly used in mass screening consist of either an historical collection of synthesized compounds owned by pharmaceutical companies or natural product collections. Each of these libraries has limitations. Historical collections contain a limited number of diverse structures (e.g., thousands of steroids, β-lactams, benzodiazepines, etc.) and, although quite useful, represent only a small fraction of the vast number of possibilities. Natural products are limited by the structural complexity of the leads identified and the (pharmaco) chemical difficulty of modifying them to useful pharmaceutical agents (e.g., taxol) endowed with the pharmacokinetic and toxicological properties required for the medical goal persued.

During the past decade, a new source of compounds has arisen, i.e., those obtained through the rapid chemical or biological generation of compound libraries. This wealth of new compounds, coupled with the ability to rapidly carry out their biological evaluation, represents an important shift in the traditional paradigm for generating and optimizing new lead structures not only for the pharmaceutical industry, but also for the agricultural, materials, and chemical industries. From its earliest days over a decade ago to the present, the field of chemical generation of molecular diversity has changed dramatically. Early attempts focused exclusively on the rapid generation of very large numbers of peptides, using solid- and solution-phase techniques. This was primarily due to the ready availability of the natural and unnatural aminoacids and the previous development of well-established coupling methodologies. The application of this approach can now rapidly generate hundreds of thousands to millions of small to medium size peptides for identifying novel leads or to help elucidate the chemical basis of known ligand–receptor interactions by preparing and evaluating a large number of peptide analogs. The new trend, however, is to focus on the generation of nonpeptide, low-molecular-weight compounds (commonly called peptidomimetic compounds). Combinatorial chemistry is one of the important new methodologies developed to reduce the time and costs associated with producing chemical diversity. Scientists use combinatorial chemistry techniques to create large populations of molecules (libraries) that can be screened efficiently en masse. By producing larger, more diverse compound libraries, companies hope to increase the probability that they will find novel compounds of significant therapeutic and commercial value. The field represents a convergence of chemistry and biology, made possible by fundamental advances in miniaturization, robotics, and biotechnology developments (15–17).

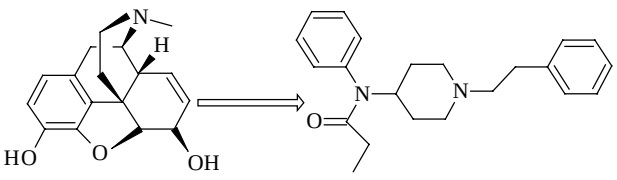

Fig. 2 It took more than 150 years to modify the complex morphine structure (left) to the simpler achiral morphinomimetic fentanyl, using classical drug-design methods.

As with traditional drug design, combinatorial chemistry relies on the progress of organic synthesis methodologies. The difference, however, is the scope: Instead of synthesizing a single compound, combinatorial chemistry exploits automation and miniaturization to synthesize large libraries of compounds (Fig. 3). Scientists then need a straightforward way to find the active ingredients within these enormous populations. Thus, combinatorial organic synthesis (COS) is not random, but systematic and repetitive, using sets of chemical "building blocks" to form a diverse set of molecular entities. Scientists have developed several different COS strategies, each with the same basic philosophy; i.e., to find ways to determine active compounds within populations, either spatially, through chemical encoding, or by systematic, successive synthesis and biological evaluation (deconvolution).

Three common approaches to COS could be envisaged. During arrayed, spatially addressable synthesis, building

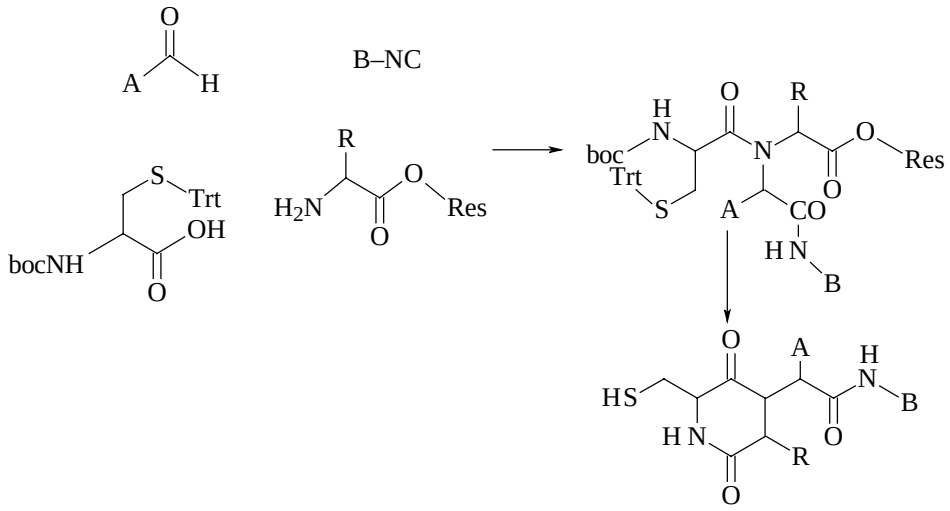

Fig. 3 Example of modular construction of a multifunctional assembly, using solid-phase synthesis technology (A and B are variable alkyl or aryl groups; boc = benzyloxycarbonyl; Trt = trityl; Res = resin).

blocks are reacted systematically in individual reaction wells or positions to form separated "discrete molecules." Active compounds are identified by their location on the grid. The second technique, known as encoded mixture synthesis, uses nucleotide, peptide, or other types of more inert chemical tags to identify each compound. During deconvolution, the third approach, a series of compound mixtures is synthesized in a combinatorial manner, each time fixing some specific structural feature. Each mixture is assayed as a mixture and the most active combination is pursued. Further rounds systematically fix other structural features until a manageable number of discrete structures can be synthesized and screened. Scientists working with peptides, for example, can use deconvolution to optimize, or locate, the most active peptide sequence from millions of possibilities.

As with traditional drug design, the ability to integrate different types of chemical, biological, and corporate information is crucial to combinatorial chemistry techniques. Combinatorial chemistry also generates an enormous amount of information, which present-day information systems still have a hard time managing. Combinatorial chemists also ask different questions in different ways, and their information systems need to adapt to find these answers quickly. For example, chemists planning a traditional synthesis typically conduct a retrosynthetic analysis to determine the best, and perhaps cheapest, way to obtain the target. In the same way, combinatorial chemists also look at retro-synthetic trees to build combinatorial libraries. Combinatorial chemists need rapid ways to access reaction information efficiently. One of the largest limitations in the construction of combinatorial libraries is in obtaining the basic building blocks necessary to run each reaction. Chemical information systems that can quickly retrieve commercially available reagents are invaluable tools in reagent acquisition.

Once built, combinatorial libraries produce unprecedented amounts of useful information, provided a consistent quality of the pharmacological evaluation can be ensured throughout the whole process. Reaction histories for each compound must be archived. Robots and other laboratory instruments need permanent monitoring, and the data they acquire have to be archived for future reference. Scientists need to integrate screening results and biological data with structural information. As in single-molecule archival systems, the archival of combinatorial libraries and their corresponding data is essential to cost-effective research and development.

Combinatorial chemistry is a promising new field that stands to revolutionize the chemical industry, and demands completely new scientific information management solutions. Combinatorial chemists will be able to meet their goals if they can find ways to plan libraries quickly, produce libraries that better interrogate biological assays, and learn from past screening results. Libraries have to be designed to systematically order and explore the wide-ranging molecular themes represented in its building block collection. Within each thematic library, subclass chemical properties are to be varied systematically in order to aid medicinal chemists in fine-tuning lead profiles. Using software that can orchestrate the planning, building, screening, and interpretation of synthesized libraries, combinatorial chemistry programs will begin to realize

their promise of minimizing the time and cost associated with bringing new molecular entities to market. Proper management of combinatorial chemistry libraries requires software applications that understand the science behind combinatorial chemistry while managing the chemical and biological data generated by combinatorial chemistry programs (18–22).

HIGH-THROUGHPUT ORGANIC SYNTHESIS (HTOS) AND HIGH-THROUGHPUT SCREENING (HTS)

The pharmaceutical world has passed through a remarkable transition in the past decade in its efforts to identify novel compounds that interact with new molecular targets and to pave the way to new therapeutic agents and product lines. The impact was first apparent in the biological sphere as assays reached the micro level and automation permitted sample throughput in multiple screens, which was unimaginable a few years earlier. HTS was born and quickly adopted as an important, if not the only, source of the initial "hits" required for the generation of leads for commercial development (23–26). The importance and permanence of the HTS focus has been manifested within the organizational structure of most corporations. Such structures tend to be immovable and only bend when economic considerations surface at both the operational and future levels. HTS is such an event. Discovery has shifted from a closed chemist–biologist relationship into a complex multidisciplinary cell that has generated a new level of professionalism within the industry. Compound management alone constitutes new positions and occasionally departments in larger organizations. This function controls the fodder that HTS requires and essentially holds the key to the success of the discovery program.

The success of HTS in uncovering the unknown parameters of a new receptor site, however, relies on access to a vast collection of compounds that possesses a very broad range of chemical functional groups dispersed in 3-D space in diverse structural frameworks. This level of diversity is rarely found in a company's archives. The development of most corporate collections has relied on acquisition from external sources. Initially, such access was primarily from universities and research institutes worldwide. The fragmentary nature of these resources spawned the creation of small industries, the compound brokers, who have served as "gofers" and data processors in the collection and marketing of such compounds. It is economically preferable for industrial groups to use these brokers and avoid the need and expense of scouring the multitude of academic archives. A significant savings over that of in-house synthesis is realized; however, the number required to come close to reasonable diversity brings the required investment again to a substantial level. It has been estimated that the average cost of $50 per sample places the overall expenditure for 100,000 compounds at ~$5,000,000 plus handling, storage, and maintenance costs. While this value can be reduced with rigorous negotiation when large numbers are purchased, the better bargain is to purchase compounds preplated on microplates. The micro requirements of most HTS assays (<10 μg) makes this latter approach especially attractive to small companies wherein acquisition and management costs of a large compound collection are prohibitive.

All of these external resources have relied heavily on the university as a primary source. An unfortunate consequence of these activities over the past decade has been a depletion of the academic resources that have accumulated over the past 50 years. Furthermore, the availability of useful quantities from current academic research has become less likely as modern chemical techniques and instrumentation permit studies with only a few milligrams. This is especially apparent in the natural product field, as the unique diversity inherent in that group has placed such acquisition at a premium. Market demands, nevertheless, persist and have led to the emergence of synthesis factories that prepare compounds specifically for the screening market, using conventional chemical techniques. Output has been greatly enhanced at some of these centers by adoption of modular approaches in synthesis. These sources have helped to fill the void in numbers, but have done little to enhance the level of structural diversity or the cost factor.

Chemists have addressed the sample resource question directly. The first approach was in the use of solid- and solution-phase techniques in the synthesis of large libraries of peptides, through combinatorial chemistry. Many discovery-based industries implemented in-house programs in combinatorial chemistry initially to explore the peptide as a supplement to their screening resources, but more recently in the use of the same technologies for the automation of general organic synthesis, as the limits and flexibility of the peptide backbone failed to satisfy the more general structural needs of discovery (Fig. 4). The success of this approach has led to the generation of a new chemical discipline, HTOS, the implementation of such programs as core technologies in many industries, and the emergence, once more, of new industries. Programs in academia also address this need, the tremendous potential it offers in the enhancement of structural diversity and the intellectual challenge of devising techniques for the

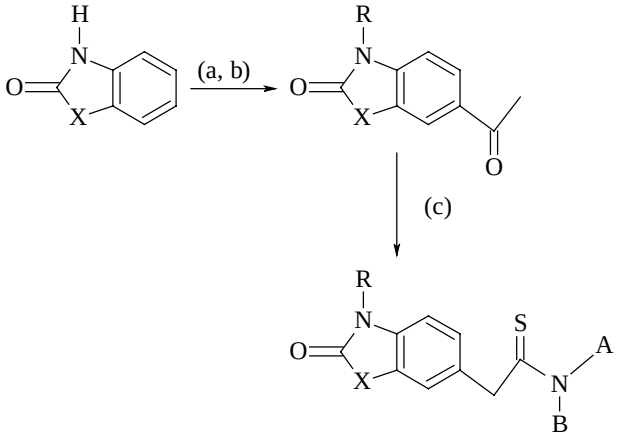

Fig. 4 Example of a three-step synthesis of a series of rather elaborated peptidomimetic compounds synthesized using straightforward reactions that can be easily automated in a fast parallel synthesis process. Methods: (a) acetic acid, polyphosphoric acid, 85°C; (b) RI, DMF, anhydrous potassium carbonate, room temperature; (c) Willgerodt–Kindler reaction (sulfur, secondary amine HNAB, DMF, 110°C).

tracking of the thousands of compounds generated as they proceed through a bioassay network. Several new industries have emerged within this specialized arena with chemical innovation and custom synthetic schemes that provide access to large chemical libraries which include features of specific interest to their client. The market and discovery impact has been dramatic.

Despite the excitement over the recent advances in HTOS development and the promises of prominent researchers in this area, HTOS cannot alone provide a diverse and sustained compound supply for screening. Today's technologies can achieve in parallel synthesis only the skeletal and functional complexity that is economically available through classical bench techniques. This aspect alone places full diversity outside the scope of HTOS because so far only a functional rather than a skeletal chemistry has been developed. Therefore, natural products still retain a commanding lead. While contributions to the enhancement of the structural diversity of a company's compound resources has, at best, been modest, the impact of HTOS on the economics of new drug development through rapid analog synthesis and the subsequent transposition of shorter development time into extended useful patent life has been dramatic. It is here that the strength of HTOS and its most important impact is felt.

The development of a lead into a product, in the traditional framework, is a stepwise process. The first stage is based on the assessment of synthetic possibilities within the limitations of organic synthesis and available starting materials, the extrapolation of preferred features defined by precedence, any structure–activity relationships (SAR) information, and guides from computational analyses. This has not changed. The next step is the orderly planning of synthesis programs within the structural goals set for the target series, the development of timelines, which integrate synthesis with information feedback from primary and secondary bioassay, and further development of the synthetic targets. Analogs of an initial lead can be prepared singly at an average rate of 100 compounds per chemist per year depending on the complexity of the chemistry involved. In the traditional mode, the number of chemists employed on a project is defined by the management according to the significance of the discovery, the complexity of the syntheses, and the intended patent scope, the primary goal being a critical assessment of market potential and, if justified, the identification of preferred candidates for further development to a marketable product. The subsequent steps involve major capital investment in toxicology and clinical study. Thus, this selection stage is critical to corporate success and, in smaller companies, may mean eventual economic survival. A reasonable time for candidate selection in the traditional mode of drug discovery has been 1–2 years. The limiting factor has generally been the initial synthesis stage and the exploration of the numerous parameters associated with SAR development. With the application of HTOS design principles and robotics in organic synthesis, we see this time shortened dramatically. The 1- to 2-year period for candidate selection can be reduced by as much as 75%. This can constitute a significant extension in useful patent life by many months.

HTOS has clearly become a new chapter in chemical technology. It brings the excitement of further growth with the resolution of the obvious challenges of conducting chemical synthesis in arrays at semimicro and submicro levels. It also significantly impacts product development in the support industries as new goals are defined in liquid handling, automation, and data management. The corollary of this restructuring is the creation of new challenges for the organic chemist, a greater dependence on multidisciplinary interactions, and the internal structure of discovery departments. It has also created new scientific and engineering challenges and product opportunities that permeate support industries. Combinatorial chemistry has become a widely used tool both for the discovery and the optimization of lead structures. The demand for quality combinatorial libraries—characterized by diversity, novelty, purity, medicinal relevance, and facile synthesis—is clearly increasing. However, most of today's libraries provide only limited novelty, owing to the use of widely available commercial reagents and standard chemistries. In a near future, to achieve this goal of

chemical diversity it will be necessary to produce truly novel high-quality, value-added libraries which comprise a wide array of pharmacophore building blocks and scaffolds, featuring a broad range of molecular properties and chemical functionality.

DNA, FUNCTIONAL GENOMICS AND PHARMACO- AND TOXICOGENOMICS

In the past few years, we have witnessed a dramatic increase in the availability of genome-scale DNA sequence information from humans and several model organisms. New technologies incorporating this information are radically altering biological research. Toxicogenomics is a new scientific subdiscipline that combines the emerging technologies of genomics and bioinformatics to identify and characterize mechanisms of action of known and suspected toxicants. Currently, the premier toxico-genomic tools are the DNA microarray and the DNA chip, which are used for the simultaneous monitoring of expression levels of hundreds to thousands of genes (27–30).

An array is an orderly arrangement of samples. It provides a mean for matching known and unknown DNA samples based on base-pairing rules and automating the process of identifying the unknowns. An array experiment can make use of common assay systems such as microplates or standard blotting membranes, and can be created by hand or make use of robotics to deposit the sample. In general, arrays are described as macro-arrays or micro-arrays, the difference being the size of the sample spots. Macro-arrays contain sample spot sizes of about 300 μm or larger and can be easily imaged by existing gel and blot scanners. The sample spot sizes in micro-arrays are typically less than 200 μm in diameter and these arrays usually contains thousands of spots. Micro-arrays require specialized robotics and imaging equipment which generally are not commercially available as a complete system.

DNA micro-arrays, or DNA (gene) chips, are fabricated by high-speed robotics on glass or nylon substrates, for which probes with known identity are used to determine complementary binding, allowing massively parallel gene expression and gene discovery studies. An experiment with a single DNA chip can provide researchers with information on thousands of genes simultaneously—a dramatic increase in throughput. Why do some drugs work better in some patients than in others? And why may some drugs even be highly toxic to certain patients? Pharmacogenomics can be regarded as the hybridization of functional genomics and molecular pharmacology. The goal of pharmacogenomics is to find correlations between therapeutic responses to drugs and the genetic profiles of patients. In the same way, toxicogenomics is the hybridization of functional genomics and molecular toxicology.

Pharmacogenomics uses genetic and genomic information to predict the response of individual patients and patient populations to drugs. Pharmacogenomics will have an impact on medicine by allowing the use of newly created genomic diagnostic tools to predict which drugs will have the greatest chance of success in treating individual patients safely and effectively. Eventually, drug prescriptions may be tailored or customized to the individual patient's genetic make-up, using this technology. Pharmacogenomics also has the potential to revolutionize the planning and design of clinical trials. By identifying which patients will respond to compounds being tested, as well as by eliminating those who may be at risk for adverse reactions, pharmacogenomics can improve the success rate of clinical development and reduce development time and cost.

The development of quantitative structure–toxicity relationships (an extended form of QSAR) to predict and to help understand the toxicity and metabolism of drugs now becomes an additional challenge for the efficient discovery of new drug candidates. Indeed, while HOTS and HTS techniques become more and more efficient to identify new lead structures and convey adequate information about the description of new pharmacophores, as such these techniques do not give direct access to compounds devoid of toxicity and endowed with the expected pharmacokinetic properties required for the therapeutic goal pursued. At this stage of the research, the professional skills and talents of experienced "traditional" medicinal chemists are again of paramount importance for the success of the whole process. A criticism that can be addressed to HOTS and HTS techniques so far developed is that, to increase potency and selectivity of the future drug candidate, relatively high molecular complexity is employed. These techniques of selection tend to unnecessarily increase molecular weight and lipophilicity and, as a result, the oral bioavailability (a major pharmacokinetic parameter) of such compounds will be inevitably very low or virtually zero. Consequently, after the discovery of initial leads, complementary programs of synthesis by traditional means are still necessary to produce grams of material necessary to assess the toxicological and pharmacokinetic properties. In this connection, while remaining somewhat empirical, the fundamental knowledge as well as the practice do exist. For this purpose, prodrugs have been intensively studied. However, this approach again tends to increase the

molecular complexity and, therefore, the molecular weight. It is, therefore, more and more envisaged to develop approaches with an integrated view of this enormous problem involving, at a very early stage, considerations of structure–toxicity and structure–metabolism relationships with the help of computerized expert systems.

The rapid evolution of the field with many techniques and disciplines involved poses the problem of the basic education and training of the personnel. While the relationship between academia and industry is frequently examined from the perspective of research and technical collaborations, it is also important to view it in terms of supply of human resources by academia to meet the demands of industry. At this level, the educational system based on the Ph.D. programs offered by universities has taken some delay with respect to the culture of the companies. A significant effort will have to be made to fill an undoubted gap in current professional education. There is also an increasing demand from the industry for basic research in organic chemistry to develop new reactions that can be employed in HOTS.

CONCLUSION

In front of the ever-increasing demand by the society and the authority for better drugs at lower cost, the pharmaceutical industry has developed sophisticated techniques of drug design, encompassing HOTS and HTS techniques to speed up the duration and the cost of drug discovery. While these techniques have not reached the level of superb maturity, they have considerably influenced the culture of the companies. However, per se these new methodologies do not directly deliver the new drug candidate, and, therefore, complementary programs of traditional medicinal chemistry are still necessary for the fine tune-up of the drug candidate. Consequently, drug design at present is made of a blend of modern technology and more classical science. The making of a blend has always been an art. It can be anticipated that in the future century drug design will evolve between these two trends, a blend of science and art in which the human being is central.

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